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Research Article

## Comparative study of transdermal nitroglycerine patch vs. intramuscular isoxsuprine in treatment of preterm labour

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### ABSTRACT

**Background:** Preterm labour and delivery are very challenging obstetric complications encountered by obstetricians. Despite advances in perinatal medicine, the incidence continues to increase. So need for best tocolytic is necessary to reduce perinatal mortality associated with preterm birth.

**Methods:** A randomized prospective comparative study, carried out over a period of 24 months. 100 antenatal cases with 24-36 weeks of gestation randomly selected & divided into two groups of 50 each. Group A: Treated with transdermal nitroglycerine patch (NITRODERM TTS-10 patch releasing 10mg / 24hr till 48 hrs.) & Group B: Treated with intramuscular isoxsuprine (Inj). Duvadilan 10 mg / 8 hrly till 48 hrs.) after treatment in both groups. Patients started on capsule Duvadilan retard (40mg) OD for one more week. Data collected regarding efficacy of the drugs in terms of Maternal side effects, Fetal side effects, prolongation of pregnancy for (48 hrs/ 48-72 hrs/3-7 days/>7 days), Changes in cervical dilatation and cervical length after 48 hrs, Mode of delivery, Gestational weeks at the time of delivery, Neonatal outcome.

**Results:** In our study there was no statistically significant difference in demographic data, risk factors, gestational age at admission, obstetric score, fetal side effects, prolongation of pregnancy, cervical length changes, successful tocolysis, gestational age at delivery, mode of delivery, neonatal outcome. But Mean cervical dilatation changes after 48 hrs. of tocolytic treatment in these two groups were statistically significant (0.14 vs. 0.19, p value = 0.024) where nitroglycerine is more effective. Headache was exclusively seen in 80% patients of nitroglycerine group & tachycardia and palpitation exclusively seen in 88% patients of isoxsuprine group, where difference is statistically significant (p value = 0.0001).

**Conclusions:** Nitroglycerine patch should be recommended over intramuscular isoxsuprine for all preterm labour patients including threatened preterm as it appears to be better tolerable in terms of treatable side effect & better acceptable than painful multiple intramuscular injections of isoxsuprine.

**Keywords:** Nitroglycerine, Isoxsuprine, Preterm, Tocolytic

### INTRODUCTION

Preterm labour is defined as the onset of labour after the age of viability (20-24) and before 37 completed weeks of pregnancy and its incidence is 6-10% of all births in developed countries.<sup>1</sup> It is common in patients with low body weight, low stature, unsupported mothers, smokers and lower social classes.<sup>2</sup> Risk factors that have been

linked to preterm delivery include cervical incompetence, haemorrhage like placental abruption, genital tract infection like bacterial vaginosis, hormonal changes due to maternal or foetal stress, multifetal pregnancy and previous history of preterm labour.<sup>3</sup>

Incidence of preterm labour is 23.3% and of preterm delivery 10-69% in India.<sup>4</sup> It is raising worldwide because of increased frequency of multiple births due to

assisted reproductive techniques (ART), more working mothers, increasing psychological stress and medically induced prematurity.<sup>4</sup> Hence the aim of the treatment for preterm delivery is to suppress the uterine contractions so as to delay the pre-term birth to allow administration of complete course of corticosteroids in order to reduce incidence of respiratory distress syndrome and to subsequently arrange in utero transfer to a center with neonatal intensive care unit facility to reduce perinatal morbidity and mortality associated with severe prematurity.<sup>1</sup>

For this purpose a wide variety of agents have been advocated like beta agonists, calcium channel blockers, prostaglandin synthetase inhibitors, magnesium sulphate and also oxytocin receptor antagonists.<sup>5</sup> Most of these drugs require strict monitoring of both mother and foetus due to their adverse effects.<sup>1</sup>

Isoxsuprine is beta adrenergic agonist that causes direct relaxation of uterine & vascular smooth muscle. Its vasodilatory actions are greater on the arteries supplying skeletal muscle than on those supplying skin. While nitroglycerine act by reducing corticotrophin releasing hormone secretion (CRH).

## METHODS

This is a randomized prospective comparative study, carried out in the department of Obstetrics and Gynaecology of K. J. SOMAIYA MEDICAL COLLEGE AND RESEARCH INSTITUTE, MUMBAI over a period of 24 months - from December 2011 to November 2013.

During a study period, 100 antenatal cases with 24-36 weeks of gestation randomly selected for study depending on following inclusion and exclusion criteria. Inclusion criteria include Pregnancy with gestational age 24 wks. To 36 wks. Uterine activity: > 3 contractions in 30 min., Cervical dilatation: os closed to 3 cm & Intact membranes. While Exclusion criteria includes Pregnancy with gestational age less than 24 wks. & more than 36 wks., Active labour with more than 3 cm cervical dilatation, Leaking per vaginum, Evidence of chorioamnionitis (i.e. fever, tachycardia, uterine tenderness, foul smelling discharge per vaginum) Pregnancy with fetal malformation, intra uterine fetal death & Contraindication for use of nitroglycerine & isoxsuprine such as known hypersensitivity, heart diseases, antepartum haemorrhages, severe anaemia, uncontrolled diabetes

**Method of study:-** A detailed history taken, dates confirmed, risk factors such as smoking, tobacco chewing, alcohol, coitus, anaemia, infection (increase in serum TLC, pus cells in urine), past h/o preterm labour, past h/o 2nd trimester abortion, cervical surgery, polyhydramnios, multiple pregnancy, Rh isoimmunisation, uterine anomalies identified. Complete

physical examination done. Vital baseline parameters like pulse, BP, temperature were recorded. Detailed per abdomen, per speculum and per vaginal examinations were done. The following investigations were done in the study subjects as soon as diagnosis was established: Hemoglobin %, Complete blood count, Urine routine and microscopy, Ultrasonography for viability, fetal biometry, placenta localization, AFI, cervical length & internal OS status done.

After inclusion & exclusion criteria met, these randomly selected eligible patients were divided into two groups

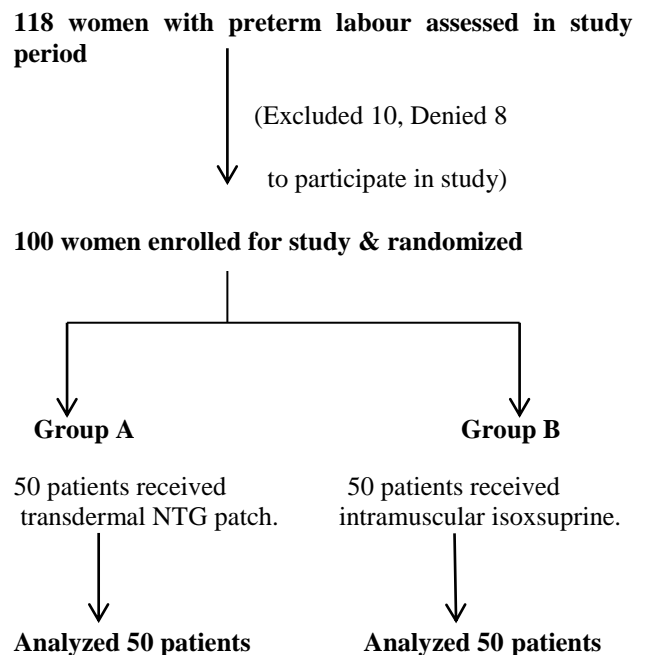
**Group A** – 50 Patients treated with transdermal nitroglycerine patch

**Group B** – 50 Patients treated with intramuscular isoxsuprine injection

Informed valid written consent was taken.

All patients enrolled in study were given inj. betamethasone (12mg) IM 2 doses 24 hrs. apart & IV antibiotics, inj. Baxim (500mg) BD & inj. Metrogyl TDS for 24 hrs. given.

Flow chart of participant selection and randomization:



### Treatment protocol:

**Group A** - Treated with transdermal nitroglycerine patch

Single nitroglycerine patch with brand name NITRODERM TTS 10 containing 50 mg of nitroglycerine which was released over a period of 24 hrs. was applied transdermally on anterior abdominal wall. The patch was removed after 24 hours and fresh patch applied for another 24 hrs. To avoid expected

hypotensive effect of transdermal nitroglycerine patch, prophylactic infusion of 500 ml of normal saline given to all the patients in the study group. Headache if occurred in nitroglycerine group is treated with T. paracetamol 500 mg single dose.

**Group B** - Treated with Intramuscular Isoxsuprine Injection

Intramuscular isoxsuprine with brand name Inj. 'Duvadilan' containing 10 mg isoxsuprine hydrochloride administered as intramuscular injection 8 hourly till 48 hrs.

Monitoring done by measuring Baseline temp, pulse, blood pressure, FHS, uterine contraction. Half hourly abdominal palpation done to note frequency and strength of uterine contractions for 2 hours, hourly for next 4 hr. , four hourly for next 18 hrs. and then 6 hourly for next 24 hrs. Pulse, BP, fetal heart rate monitoring every 15 min for 2 hours, hourly for next 4 hrs., four hourly for 18 hrs. and then 6 hourly for next 24 hrs. Close monitoring done for maternal side effects such as headache, palpitation, flushing, giddiness, and some side effect specific to transdermal nitroglycerine patch like local irritation. & Fetal side effects such as fetal distress i.e. FHS < 110 bpm and fetal tachycardia i.e. FHS > 150 bpm. Per vaginal examination done if uterine contractions persist for > 12 hrs. or c/o leaking per vaginum or after 48 hrs. & cervical length assessment by USG repeated after 48 hrs.

Treatment was discontinued in both the groups if there was Maternal tachycardia greater than 120 beats/minute, Drop of blood pressure by 15 mm of Hg or more from baseline diastolic pressure, Signs and symptoms suggestive of pulmonary oedema such as breathlessness, cough with expectoration.

Patients were discharged 48 hrs. after uterine contractions subsided and started on oral beta mimetic isoxsuprine (40mg) sustained release capsule continued till one more week and patient assessed antenatally every week until delivery.

Successful endpoint: Treatment was considered successful if uterine contractions subsided and thus tocolysis achieved for more than 48 hours.

Data collected regarding efficacy of the drugs in terms of Maternal side effects, Fetal side effects , Prolongation of pregnancy for 48 hrs., Changes in cervical dilatation and cervical length after 48 hrs., Prolongation of pregnancy, Mode of delivery, Gestational age at the time of delivery, Neonatal outcome & birth weight.

## RESULTS

Total number of deliveries during the study period was 3126, Total number of preterm labour cases was 292, and therefore Incidence of preterm labour was 9.34%.

In our study, majority of patients (38%) are from age group 16-20 yrs. More than 60% of the study population was illiterates in both groups (64% vs. 66%). Total illiterate patients were 65 out of 100 i.e. 65%. Patients were categorized in different class depending upon kuppaswamy's6 classification. Majority of the patients in our study came from lower socioeconomic status in both groups (30 % vs. 26 %). In our study, incidence of preterm labour was more in primigravida (56%) than multigravida (44%). Majority of the patients in our study were between 31-33.6 weeks of gestation 44% in nitroglycerine group and 48% isoxsuprine group respectively. The mean gestational age at admission in nitroglycerine group and isoxsuprine group is  $32.53 \pm 1.6391$  and  $32.09 \pm 1.9696$  weeks respectively. In our study commonest risk factor in nitroglycerine and isoxsuprine groups is anaemia (18 % vs. 20 % respectively), followed by infection (12% vs. 18% respectively) among total 15 patients of infection 10(66.66%) patients had UTI. History of preterm labour (4% vs. 8% respectively) and polyhydramnios (4% vs. 6% respectively) and etc.

In patients with successful tocolysis, mean cervical dilatation changes in nitroglycerine group is  $0.14 \pm 0.64$  cm and in isoxsuprine group it is  $0.19 \pm 0.89$  cm, which is statistically significant (p value=0.024) as shown in Table no.1 but there are no statistically significant changes seen in ultrasound estimation of cervical length (on admission & 48 hrs. after starting therapy) as shown in Table no.2.

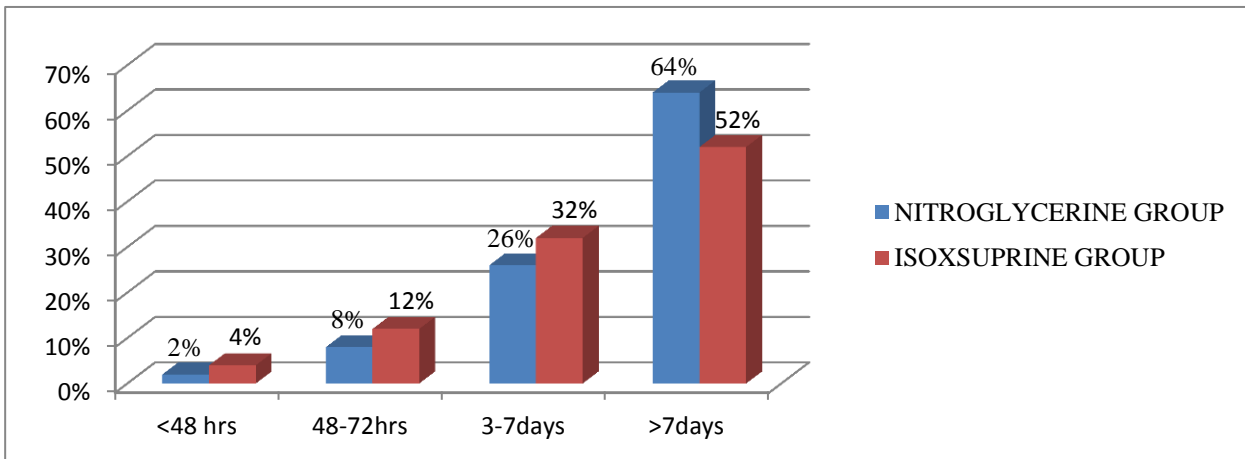
**Table 1: Changes in cervical dilatation.**

Cervical dilatation (cm)		Nitroglycerine group	Isoxsuprine group	Statistics
At admission (N=50,I=50)	Mean	1.08	1.15	P value = 0.7371
	Standard deviation	0.81	0.85	
After 48 hrs. (N=49,I=48)	Mean	1.22	1.34	P value = 0.4712
	Standard deviation	1.1	1.26	
Dilatation changes (N=49,I=48)	Mean	0.14	0.19	P value = 0.02481
	Standard deviation	0.64	0.89	

**Table 2: Changes in cervical length.**

Cervical length		Nitroglycerine group	Isoxsuprine group	Statistics
At admission (N=50,I=50)	Mean	2.788	2.814	P value = 0.670
	Standard deviation	0.3173	0.2900	
After 48 hrs. (N=49,I=48)	Mean	2.69	2.64	P value = 0.675
	Standard deviation	0.566	0.657	
Cervical length changes (N=49,I=48)	Mean	0.1122	0.1979	P value = 0.369
	Standard deviation	0.38223	0.54009	

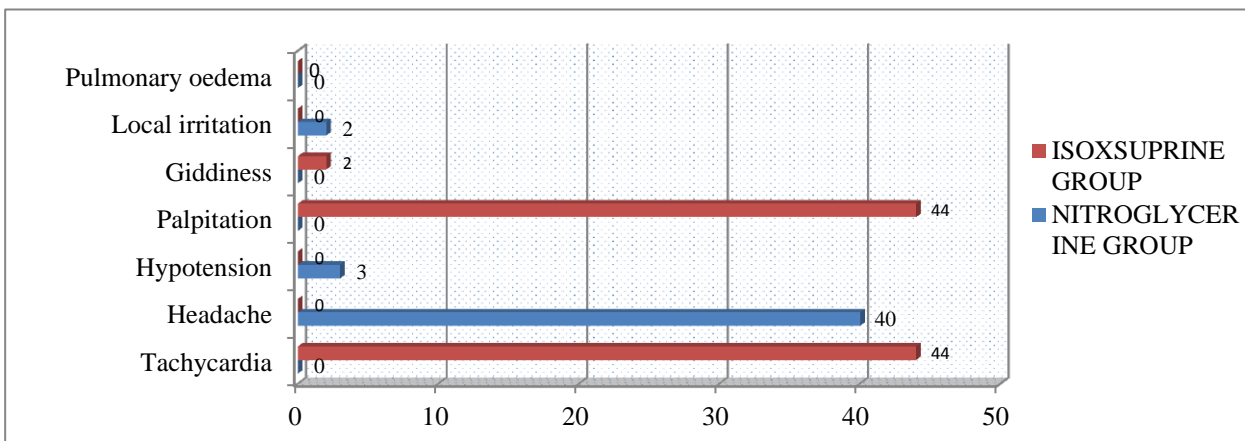
Test applied: Independent T-test



**Figure 1: No. of Patients delivered.**

**Table 3: Success or failure of tocolysis.**

	Nitroglycerine group		Isoxsuprine group		Statistics
	No. of patients	%	No. of patients	%	
Successful tocolysis	49	98 %	48	96 %	Test applied: Fisher's exact test
Failure of tocolysis	1	2 %	2	4 %	
Total	50	100%	50	100%	P value = >0.99



**Figure 2: Maternal side effects.**

Fetal distress (FHS < 110 bpm) was seen in 1 out of 50 patients of nitroglycerine group and 1 out of 50 patients of isoxsuprine group, Fetal tachycardia (FHS > 150 bpm) was seen in 5 out of 50 patients of nitroglycerine group and 7 out of 50 patients of isoxsuprine group, the difference is not statistically significant.

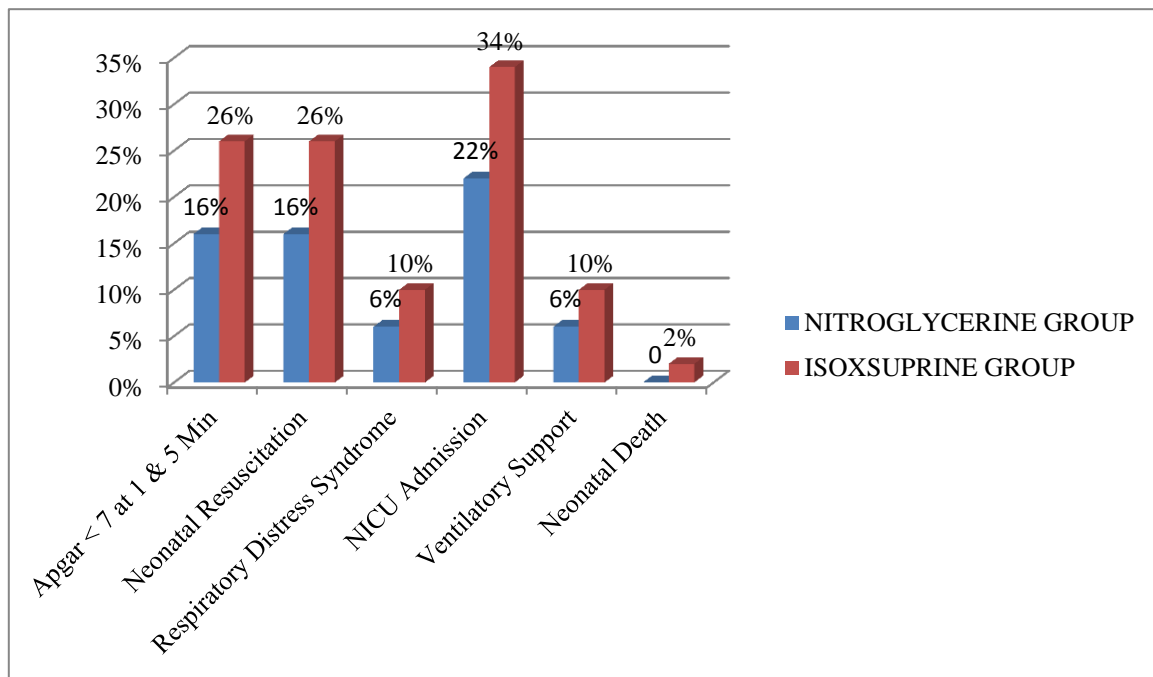
Number of patients delivered in < 48hrs / 48 -72 hrs / 3-7 days / > 7days is comparable i.e. prolongation of

pregnancy is similar in both groups and statistically not significant as shown in Figure no. 1. Mean duration of prolongation of pregnancy in nitroglycerine group was 24.32 ± 19.611 days and in isoxsuprine group was 20.52 ± 17.561 days but difference was statistically not significant. In our study tocolysis therapy is successful in 98% cases in nitroglycerine group as compared to 96% success rate of isoxsuprine group. But difference is statistically not significant (Table no. 3).

**Table 4: Maternal side effects.**

Side effects	Nitroglycerine group		Isoxsuprine group		Statistics
	No. of pts.	%	No. of pts.	%	
Tachycardia	0	0 %	44	88 %	P value= 0.0001
Headache	40	80 %	0	0 %	P value= 0.0001
Palpitation	0	0 %	44	88 %	P value= 0.0001
Hypotension	3	6 %	0	0 %	P value = 0.242
Giddiness	0	0 %	2	4 %	P value = 0.495
Local irritation	2	4 %	0	0 %	P value = 0.495
Pulmonary oedema	0	0	0	0	

Test applied: Pearson's Chi-square tests  
Test applied: Fisher's exact test



**Figure 3: Neonatal Outcome.**

In our study, out of 50 patients, headache was noted in 40(80%) patients of nitroglycerine group as compared to isoxsuprine group where none of them had Headache. Here p value is < 0.05 that is statistically significant. Out of 50 patients, tachycardia and palpitation were noted in 44(88%) patients of isoxsuprine group as compared to nitroglycerine group where neither of them tachycardia

nor palpitation had. Here p value is < 0.05 that is statistically significant. Other side effects like giddiness noted in 2(4%) patients of isoxsuprine group and hypotension and local irritation noted in 3(6%) and 2(4%) patients of nitroglycerine group respectively. Difference in these side effects is statistically not significant. No other serious side effects noted in both groups. As shown in Table no. 4 & Figure no. 2

Mean gestational age at delivery in nitroglycerine group was  $36.16 \pm 2.645$  wks. and in isoxsuprine group was  $35.16 \pm 2.930$  wks. Difference is statistically not significant. Patients delivered beyond 37 weeks were 38% in NTG group and 26% in isoxsuprine group. Out of 50 patients in nitroglycerine group, 38 patients (76%) and out of 50 patients in isoxsuprine group, 36 patients (72%) delivered vaginally. 9 patients (18%) in nitroglycerine group and 11 (22%) patients in isoxsuprine group required caesarean section. In both groups 3 patients (6%) delivered vaginally by instrumental delivery. Difference is statistically not significant.

In our study, mean birth weight of infants delivered is  $2.506 \pm 0.42877$  kg in nitroglycerine group and  $2.34 \pm 0.44309$  kg in isoxsuprine group. This difference is statistically not significant. Overall mean birth weight is 2.423 kg. Difference in the variable of neonatal outcome was statistically not significant & comparable in both groups as shown in Figure no.3.

## DISCUSSION

Successful tocolysis is defined as prolongation of preterm labour beyond 48 hrs. and failure of tocolysis is defined as delivery within 48 hours. In patients with successful tocolysis, mean cervical dilatation changes in nitroglycerine group is  $0.14 \pm 0.64$  cm and in isoxsuprine group it is  $0.19 \pm 0.89$  cm, which is statistically significant. Even the mean cervical dilatation changes in nitroglycerine group was statistically significant compared to isoxsuprine group, it is not clinically significant as it was not crossing  $> 3$ cm cervical dilatation. In our study, majority of patients have insignificant mean cervical length (effacement) changes, thus indicating successful tocolysis. This was seen in both the groups. Thus mean cervical length compared in both group and it was not significant hence both the drugs are equally good in halting progression of cervical length.

In our study we get mean prolongation of pregnancy in nitroglycerine group by  $24.32 \pm 19.611$  days which is comparable with study conducted by He Q et al<sup>7</sup> and Smith et al<sup>8</sup> which is 25 days and 23 days respectively. So mean prolongation of pregnancy with nitroglycerine is comparable with above mentioned studies. While mean prolongation of pregnancy in our study was  $20.52 \pm 17.561$  days with intramuscular isoxsuprine. This result was similar to those reported by Rayamajhi et al<sup>9</sup> study. Rayamajhi et al<sup>9</sup> reported mean prolongation of pregnancy as 19.18 days with isoxsuprine. So mean prolongation of pregnancy with isoxsuprine is comparable with above mentioned studies.

In our study success rate is 98 % in patients treated with nitroglycerine patch. Success rate of transdermal nitroglycerine is comparable with study conducted by Sachan Rekha et al.<sup>10</sup> (98%). In our study success rate is 96 % in patients treated with isoxsuprine & is comparable with study conducted by Sachan Rekha et al.<sup>10</sup> Success

rate is comparable with above mentioned study. In nitroglycerine group, out of 50 patients, 1 patient & in isoxsuprine group, out of 50 patients, 2 patients who delivered were already 2.5 to 3 cm dilated with good uterine activity. So to prevent preterm delivery we should pick up preterm in early stage.

In our study, headache was exclusively seen in nitroglycerine group in which it occurred in 80% of patients, headache is relieved by giving oral T.paracetamol and all patients responded to paracetamol tablet. Local irritation occurred in 4 % patients and hypotension in 6 % patients. In our study, tachycardia and palpitation were exclusively seen in isoxsuprine group in which both occurred in 88% of patients and giddiness in 4 % patients. None of the patient had pulmonary edema. In a study conducted by Sachan Rekha et al (2012),<sup>10</sup> headaches are exclusively seen in nitroglycerine group in 100 % cases while tachycardia and palpitation are exclusively seen in isoxsuprine group 100 %. So our study is comparable with above mentioned study as headache is exclusive side effect of nitroglycerine group and tachycardia and palpitation are exclusive side effects of isoxsuprine group.

## CONCLUSIONS

Nitroglycerine and isoxsuprine, both drugs are effective in controlling uterine activity and thus preterm labour for first 48 hrs. To be effective, both nitroglycerine and isoxsuprine drug should be started in early preterm labour. Hence preterm labour should be diagnosed as early as possible.

Although nitroglycerine and isoxsuprine are safe and effective drugs in preventing preterm labour, nitroglycerine appears to be better tolerated by patients as compared to intramuscular isoxsuprine. Headache which is seen in nitroglycerine group is treatable with tablet paracetamol and is better tolerable than tachycardia and palpitation which are common side effects of isoxsuprine. Nitroglycerine as a single dose patch application per day is better acceptable than multiple intramuscular injections of isoxsuprine. Hence, nitroglycerine patch should be the first choice of tocolytic agent for all preterm labour patients including threatened preterm, especially for first 48 hrs.

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